REMARKS

Election/Restriction

Applicant acknowledges that the Examiner has made the restriction requirement FINAL. Applicants maintain the right to file one or more divisional or continuation applications directed to unelected subject matter.

Amendments to the Claims

Claim 1 has been amended to insert the phrase "B-2036 of [SEQ. ID. NO. 1]" after "growth hormone antagonist receptor". Support can be found in claims 35-38 as originally filed and as exemplified in the Examples.

Claims 2 – 34 and claims 39 – 68 have been amended to replace the word "embodiment" with "claim" as suggested by the Examiner.

Claims 35 – 38 have been cancelled and the limitation added to claim 1. The dependency of Claims 39 – 44, 49, 50, 53, 54, 57, 58, 63, and 64 depending from Claims 35 – 38 has been amended to recite the parent claim from which Claims 35 – 38 depended.

Objections to Specification

The Examiner objected to the specification under 37 CFR 1.58(a) for containing flowcharts.

As required by the Examiner applicant has amended the specification in accordance with 37 CFR 1.81 to insert paragraphs to describe the Figure 2a-d and Figure 3a-c, delete pages 78 – 81 and 84 – 86 containing Flowchart 1 and Flowchart 2, amended Examples 1-5 to refer to Figure 2a-d and Figure 3a-c, and applicant has submitted

herewith in the APPENDIX beginning after page 21, Figure 2a-d and Figure 3a-c containing Flowchart 1 and Flowchart 2 as originally filed as part of the specification.

Claim Rejections – 35 USC § 103

Claims 1-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jespersen, et al., Eur. J. Biochem., 1994, 219, 365-373, in view of US patent 5,849,535 issued to Cunningham, and further in view of Houk, et al., J. Am Chem. Soc., 1987, 109, 6825-6836.

The Examiner argues Jespersen, et al., teaches the characterization of a trisulfide derivative of human growth hormone produced in E. Coli and uses 1,4-dithiothreitol to reduce the full-length derivative of the growth hormone. The Examiner states that the trisulfide bond could be formed by a HS^- attack on a disulfide linkage of the cysteine. The Examiner concedes that the reference does not teach the pegylation of the protein and use of functional equivalents of other mercapto reducing agents, and does not teach using the method for reducing the trisulfide impurity for antagonist.

The Examiner asserts Cunningham, et al., discloses a method for the preparation human growth hormone antagonist, B-2036 variants, that encompass the pegylation of the growth hormone . The Examiner concedes that Cunningham, et al. does not use mercapto compounds as reducing agents.

The Examiner argues Houk, et al., discusses the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The Examiner contends that the list of compounds can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages.

The Examiner concludes that the method of purification that worked for the growth hormone should work for the antagonist. The Examiner also presumes there would have been reasonable expectation of success given the knowledge that presence of mercapto

compounds reduces the trisulfide impurity in the growth hormone produced from E. Coli and can be pegylated using the method taught by Cunningham, et al. Therefore, it would be prima-facie obvious to combine the teachings of Jespersen, Cunningham and Houk to develop method for the production of growth hormone antagonist from E. Coli with reduced presence of trisulfide impurity.

To establish a *prima facie* case of obviousness, the USPTO must satisfy three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated one of ordinary skill in the art to modify a reference or combine references. Second, the proposed modification must have had a reasonable expectation of success. Finally, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *See* MPEP §2142; *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Applicant respectfully submits that the Office has failed to establish a *prima facie* case of obviousness because the Office has failed to establish the incentive in the references to combine the references, that there is a reasonable expectation of success, and all of the limitations of the claims.

The Examiner relies on Jespersen to establish the use of 1,4-ditiothreitol to reduce the trisulfide of human growth hormone. As the Examiner points out the use of functional equivalents of other mercapto reducing agents is not taught by Jespersen and Jespersen does not teach using the method for reducing the trisulfide impurity for an hGH antagonist. To overcome the shortcomings of Jespersen the Examiner relies upon Cunningham to establish the purification of B-2036 (hGH antagonists) but concedes that Cunningham, et al. does not use mercapto compounds as reducing agents. The Examiner relies on Houk, et al., to provide the structure-reactivity relations for number of thiol compounds, which are functional equivalents of the compounds recited the instant application. The Examiner contends that the list of compounds (on pages 6830 and 6831) can be used individually or in combinations of others for the purpose of reducing the disulfide bonds or trisulfide linkages. The Office concludes that there would have been reasonable expectation of success to use a mercapto compound to decrease the levels of trisulfide in an hGH antagonist.

The teaching of Jespersen does not support the Examiner's position that there would have been a reasonable expectation of success. To the contrary Jespersen states:

> *"To our knowledge trisulfide bond formation in proteins has not previously been described."* (p. 372, col. 1, 5th paragraph).

B-2036 is an entirely different protein from hGH and as the Examiner points out B-2036 has nine amino acid changes compared to hGH. Cunningham fails overcome the shortcomings of Jespersen and fails to establish that trisulfides even exist in B-2036 and as the Examiner concedes Cunningham, et al. does not use mercapto compounds as reducing agents indicating that Cunningham didn't even recognize the problem. Where the art teaches that something is an extremely rare event it does not support the notion that there was a reasonable expectation for success. Furthermore, Jespersen states:

> *"The **mechanism of trisulfide formation** in the minor loop of BhGH is **unknown*** (p. 372, col. 1 last paragraph - emphasis added),
>
> and
>
> *". . .it **could** be cleaved by HS^- in a disulphide exchange reaction forming a hydrogen disulphide derivative of one of the cysteines, which then **could** react with the free cysteines to form the small loop trisuphide bond* (p. 372, col. 2, first sentence – emphasis added).,

which can't be construed as indicating there is a reasonable expectation of success when the problem isn't even understood. The teachings of Houk also fail to overcome the shortcomings of the teachings Jespersen and Cunningham. Applicant's can find no reference to **trisulfide bonds** in proteins in Houk as alleged by the Examiner.

Conclusion

Claims 1-34 & 39-68 are pending. Claims 69-76 have been withdrawn. Claims 35-38 have been cancelled. No new matter has been added. In view of the foregoing amendments and arguments, it is respectfully submitted that all claims now pending in the present application are in condition for allowance. Therefore, swift passage of the application and claims to issue is respectfully requested.

Respectfully submitted,

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Attachments: Figures 2a-d & 3a-c